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Determinants of Under-Five Childhood Diarrhea in Kotebe Health Center, Yeka Sub City, Addis Ababa, Ethiopia: A Case Control Study

By Aklilu Tilahun Zeleke & Zewdie Aderaw Alemu
Debre Markos University, Ethiopia

Abstract- *Background:* It is a fact that diarrheal diseases caused major public health problem in children under-five years of age, especially in developing countries like Ethiopia. The objective of this study was to investigate the association of socio demographic, behavioral and environmental factors with under five diarrhea in Kotebe area, Yeka sub city, Addis Ababa.

Methods: Institutional based unmatched case-control study design was conducted. A case in this study was a child under-five years of age visited Kotebe health center for treatment and a control was a child under-five years of age without diarrhea that came to the center for vaccination and treatment of other cases. A face-to-face interview based on a pre-tested, structured questionnaire was conducted with mothers/ caretakers with trained nurses.

Keywords: *unmatched case-control, under-five child-hood diarrhea, yeka sub city, kotebe health center, addis ababa.*

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Determinants of Under-Five Childhood Diarrhea in Kotebe Health Center, Yeka Sub City, Addis Ababa, Ethiopia: A Case Control Study

Aklilu Tilahun Zeleke [α] & Zewdie Aderaw Alemu [σ]

Abstract- ***Background:*** It is a fact that diarrheal diseases caused major public health problem in children under-five years of age, especially in developing countries like Ethiopia. *The objective of this study was to investigate the association of socio demographic, behavioral and environmental factors with under five diarrhea in Kotebe area, Yeka sub city, Addis Ababa.*

Methods: Institutional based unmatched case-control study design was conducted. A case in this study was a child under-five years of age visited Kotebe health center for treatment and a control was a child under-five years of age without diarrhea that came to the center for vaccination and treatment of other cases. A face-to-face interview based on a pre-tested, structured questionnaire was conducted with mothers/ caretakers with trained nurses. Binary logistic regression analysis was used to measure the association between dependent and independent variables, calculating odds ratios and 95% confidence intervals. Statistical significance was set at $\alpha \leq 0.05$. Multivariable analyses were applied to identify the relative effect of explanatory variables on the dependent variable.

Result: A total of 350 study subjects, including 117 cases and 233 controls, were recruited into the study. The study revealed that some factors remained independently associated with the risk of diarrhea, namely age of the children AOR (95%CI); 4.22 (1.36-13.14), maternal education AOR (95%CI); 0.33 (0.16-0.65), supplementary feeding commencing time AOR (95%CI); 0.30 (0.09-0.95) and hand washing after cleaning child bottom AOR (95%CI); 0.59 (0.35-0.99) with p-value ≤ 0.05.

Conclusion: From this study, associated factors of diarrhea were identified. The finding is important for health intervention and supports the view that investing in girls' education has substantial benefits on child health.

Keywords: unmatched case-control, under-five childhood diarrhea, yeka sub city, kotebe health center, addis ababa.

I. Introduction

Diarrhea is a global problem, but is especially prevalent in developing countries in conditions of poor environmental sanitation, inadequate water supplies, poverty and limited education (1). In developing countries, approximately 2 million people, the vast majority of whom are under-five children, die from diarrhea each year (2). The Iraq study showed that diarrhea was associated with age of child, area of residence, maternal education, a source of water, toilet (3). Demographic and socioeconomic factors, including age of the child, religion, ethnicity, level of education, marital status, and number of children, mother's job and income of the family. The positive correlation between maternal education and child health outcomes is well established. One study in Bangladesh showed that a child whose mother completed primary school is 20% more likely to survive than a child whose mother has not received any formal schooling, and a child born to a mother who attended secondary school is 80% more likely to survive (4). Environmental determinant factors include a source of water, water treatment, latrine availability, latrine ownership, waste water disposal, refuse disposal, separate house for domestic, and adult member defecation. Diarrheal disease due to unsafe water and lack of sanitation are the biggest cause of morbidity and mortality in under-five children in the world especially in poor countries (5). A child dies every 15 seconds from diarrhea caused largely by poor sanitation and contaminated water supply (6). Behavioral factors of diarrhea include hand washing time, hand washing habit, supplementary feeding time, method of feeding, and measles immunization. Behavioral factors associated with acute childhood diarrhea include lack of hand-washing, poor infant and young child feeding practices and lack of child immunizations (7). Therefore, the objective of this study was to assess diarrheal associated socio demographic, environmental and behavioral determinants of acute childhood diarrhea factors among children aged under five years.

II. Methods

Institutional unmatched case-control design was used to assess the determinants of under five diarrhea from February to March 2014 in Kotebe health center, Yeka sub city, Addis Ababa. The population of Yeka is the largest of all sub cities in Addis Ababa which is 346,484. The proportion of under -five children in the Yeka sub city is 5.4%. Diarrhea prevalence is 9.4% in Addis Ababa (8).

The source population was under-five children attending at Kotebe health center. Study population

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includes selected children less than five years of age who visited Kotebe health center. Study units were samples of under five children with diarrhea for cases and without diarrhea for controls who visited Kotebe health center.

The sample size calculation was based on the following assumptions: P1=proportion of diseased with disposal of refuse in the pit; P2= proportion of non-diseased with disposal of refuse in the pit. From a similar study conducted in Nekemte town with refuse disposal method as the main predictor of outcome (diarrhea), the sample was 42.86% of cases and 61.47% of the control (9). *Therefore, P1=0. 4286, z1=1. 96 (95% CI) and P2=0. 6147, z2=0. 84 (power of 85%) the proportion of case and control was assumed to be 1:2.* Ten percent non-response rate, the total sample was estimated using Epi Enfo ™ 7.1.0.6 software as 350 (Cases=117, Control=233).

A structured questionnaire was developed to collect information on socio demographic and economic characteristics, environmental conditions and behavioral aspects for both cases and controls. Since the children were too young at under five years of age to be interviewed, verbal consent was taken from the mothers or caregivers.

Diarrheal children less than five years of age visited Kotebe health center were recruited into the study after their parents expressed the willingness to participate in the study. To ensure that cases selected for the study represented a homogeneous entity, a definition of diarrhea was established. In addition, the age of a child was verified by cross-examining the information provided on their health and vaccination cards, or by the confirmation of the mother.

In this study, non-diarrheal patient children and those who came for vaccination with the age of less than five years admitted to Kotebe health center between February to March 2014 were selected into the study. The recruitment of controls was carried out after their parents consented to participate in the study. Finally, like cases, the parents were more likely to be willing to cooperate than the parents of healthy children, thus minimizing bias due to non response.

The questionnaire was developed after reviewing relevant literatures to the subject to include all the possible variables that address the objective of the study. The questionnaire was first prepared in English and then translated to Amharic and back translated to English to maintain the consistency of the contents of the instrument. Data collectors were trained and closely supervised during data collection. The training mainly focused on interviewing techniques. Frequent communication between the research team was conducted.

The pre-testing of the questionnaires was conducted on five percent of the questionnaires before data collection. After conducting pre-testing, some change in the questionnaire was made. On the measles vaccination status of children, in some cases mothers could not remember exactly whether children had vaccinated or not. Therefore, for example, mothers were asked whether (or not) their children had been vaccinated on the ninth month (ninth month vaccination). The completed questionnaires were checked every day during data collection for completeness, clarity and consistency.

In the study, the occurrence of diarrhea in a child was considered to be the dependent/outcome variable. Environmental factors (a type of water source, availability and ownership of toilet facility, solid and liquid waste disposal method), socio demographic (age, sex, religion, ethnicity, family size, educational status, and maternal job) and behavioral factors (hand washing, supplementary feeding commenced, and measles immunization) as exposure/independent variables.

The data were entered and analyzed using SPSS version 20. Descriptive statistics (frequencies, proportion, measures of central tendencies and variations were obtained and displayed mainly on the tables and word expressions) were used to describe the study population in relation to relevant variables. The odds ratio was computed to see the strength of association. To identify independent predictors of childhood diarrhea, only variables that were statistically significant during bivariate test were entered into multiple logistic regression models to control the effect of confounders. P≤0. 05 was considered statistically significant. Results were reported as the adjusted odds ratio (AOR) and 95% confidence intervals.

The necessary ethical consideration was made before the actual data collection took place. Written consent was obtained from the ethical clearance committee of Debre Markos University medicine and the health Sciences College. Written Ethical approval and letter of permission were obtained from the concerned bodies of Addis Ababa city health bureau, sub city health office, and woreda health office officials. Before each interview, participants were provided with an explanation of the purpose of the study and its procedures. Participation (which includes mothers/caretakers) in the study was totally voluntary. They were not forced or persuaded to participate in the study. Informed verbal consent was obtained from the mothers/caretakers of the children. Privacy and confidentiality were maintained during the interview. Since the study was conducted by asking mothers of children recruited to gather information, the conduct of the study did not pose any health risk to the participants. Mothers who were found that their children were sick during the study time were consulted about the causes of the disease and her knowledge about it.

III. Results

A total of three hundred and fifty respondents was included in the study with a response rate of 100%. Of the total children, 184 (52.57%) were female. There were 55 (47%) case male and 62 (53.0%) case female. Cases were mostly children between 6 and 11 months (41%). One hundred and twenty nine (36.9%) under five children were within 12-24 months age category.

More than half of respondents 182 (52.0%) had 2-3 family size. The majority of the respondents (mothers or caregivers) 265 (75.71%) were Orthodox Christian by religion and Amhara 199 (56.86%) by ethnic group.

One hundred and thirty eight (39.4 %) mothers had secondary education and 225 (64.29%) were housewives. *Of the total cases, 32 (27.4%) fell in illiterate category and the least number of cases was found 13 (11.1%) in college/university category.*

Table 1 : Socio-demographic and economic characteristics of diarrhea among children under 5 years of age in Yeka sub city, Addis Ababa, 2014 (n=350)

Variables	Category	Total	
		Frequency	%
Age of child (months)	<6	45	12.9
	6-11	115	32.9
	12-23	129	36.9
	24-59	61	17.4
Sex of child	Male	166	47.43
	Female	184	52.57
Family number	2-3	182	52
	4-6	158	45.14
	7-10	10	2.86
Religion	Orthodox	265	75.71
	Muslim	39	11.14
	Protestant	46	13.14
Ethnicity	Oromo	76	21.71
	Amhara	199	56.86
	Tigrie	30	8.57
	Guragie	32	9.14
	Others	13	3.71
Maternal education	Illiterate	81	23.0
	Able to read and write	27	7.70
	Primary (1-8)	71	20.30
	Secondary (9-12)	138	39.40
	College/University	33	9.43
Occupation of Mother	House wife	225	64.29
	Daily laborer	20	5.71
	Farmers	3	0.86
	Employee	97	27.71
	Others	5	1.43
Marital status	Married	316	90.3
	Single	9	2.6
	Divorced	13	3.7
	Widowed	6	1.7
	Separated	6	1.7

The majority of respondents, 302 (86.29 %) in the area used tap as the main source of water. Only 1.43 % used unprotected well as a source of water. About 243 (69.43%) of the study population had shared latrine. Almost all respondents 349 (99.71) had latrine. Most respondents 261 (74.57%) dispose solid waste in garbage, whereas only 3 (0.86%) in open fields. More

than half of the respondents dispose liquid waste in sewage system 180 (51.58%).

Table 2 : Environmental exposure characteristics of diarrhea among children under 5 years of age in Yeka sub city, Addis Ababa, 2014. (n=350)

Variables	Category		Total	
			Frequency	(%)
Water source	Piped water		302	86.29
	Protected well/spring		43	12.29
	Unprotected well/spring		5	1.43
Latrine Owned	Private		107	30.57
	Shared		243	69.43
Latrine Availability	No		1	0.28
	Yes		349	99.71
Disposal of household/solid wastes	Open field	No	347	99.14
		Yes	3	0.86
	Pit	No	332	94.86
		Yes	18	1.84
	Burning	No	283	80.86
		Yes	67	19.14
	Garbage can	No	89	25.43
		Yes	261	74.57
Disposal of wastewater	Sewage system	No	180	51.58
		Yes	170	48.60
	Pit	No	186	53.14
		Yes	164	46.86

Out of those mothers/caretakers who started supplementary feeding for their children 70 (20.1%) started before the child reached 6 months, and 109 (31.2 %) at the age of 6 months and 134 (38.4%) mothers breastfed their children exclusively that means they started after six months. Only 36 (10.3%) did not start any supplementary food before six months. Inconsistent with EDHS 2011 (93.5%), the majority of respondents (95.6%) explained that their children were vaccinated for measles. Only 91 (26%) of the mothers/care givers had used only water to wash their hands, whereas 341 (97.43 %) used both water and soap to wash their hands.

Table 3 : Behavioral factors for diarrhea among children under 5 years of age in Yeks sub city, Addis Ababa, 2014. (n=350)

Variables	Category		Total	
			Frequency	%
Supplementary feeding commenced	<6 (not yet started)		36	10.28
	Before 6 months		70	20
	On 6 months		109	31.20
	After 6 months		134	38.4
Measles Vaccination	No		11	4.3
	Yes		242	95.6
Hand washing substitutes	Water only	No	259	74
		Yes	91	26
	Water, Soap & substitutes	No	9	2.57
		Yes	341	97.43
	Others	No	348	99.4
		Yes	2	0.57
Hand washing time	After defecation	No	20	5.71
		Yes	330	94.29
	After cleaning child's bottom	No	167	47.71
		Yes	183	52.29

	Before handling food	No	12	3.4
		Yes	338	96.6
	Before feeding children	No	50	14.3
		Yes	300	85.7
	Other	No	342	97.71
		Yes	8	2.29

Factors Associated with the Occurrence of Childhood Diarrhea

Table 4 presents selected socio-demographic, environmental and behavioral determinants of the mothers or care givers in relation to under-five diarrhea.

The occurrence of childhood diarrhea had association with the age of under-five children. The crude odds ratio showed that diarrhea is highest in the age group 6-11 months (COR [95% CI] =4. 66 [1.83-11.87]) and 12-23 months (COR [95% CI] =3. 73 [1.47-9.50]) and the reason for this might be, at these stages, the children could try to detect their surroundings so that they could be exposed to the case. It is least for 0-6 months of age. Comparing with illiterate, higher levels of education of mothers, such as secondary, were associated with a lower occurrence of diarrhea. In other words, OR decreased inversely in proportion to higher levels of education of mothers (COR [95% CI] = 0.37 [0.20-0.69]).

An association has been found between supplementary feeding commenced, and the occurrence of diarrhea among under five children. The odds of the occurrence of childhood diarrhea among children who started supplementary feeding before six months was around four times [COR: 3.77, 95% CI: (1.60-9.20)] higher when compared with those less than six months and not started a supplementary food yet. An association has been found between hand washing after cleaning the child's bottom and diarrhea among under five children [COR: 0.56, 95% CI: (0.36-0.88)].

Table 4 : Factors associated with diarrhea among children under 5 years of age in Yeks sub city, Addis Ababa, 2014 (n=350)

Variables	Category	Case n (%)	Control n(%)	COR(95%CI)	AOR(95%CI)
Age of child (months)	<6	6 (5.1)	39 (16.7)	1.00	
	6-11	48 (41.0)	67 (28.8)	4.66 (1.83-11.87)*	4.22 (1.356-13.14)†
	12-23	47 (40.2)	82 (35.2)	3.73 (1.47-9.50)*	3.09 (0.97-9.88)
	24-59	16 (13.7)	45 (19.3)	2.31 (0.82-6.48)	2.45 (0.66-9.10)
Maternal education	Illiterate	32 (27.4)	49 (21)	1.00	1.00
	Able to read and write	16 (13.7)	11 (4.7)	2.22 (0.92-5.41)	1.95 (0.75-5.09)
	Primary (1-8)	29 (24.8)	42 (18)	1.06 (0.55-2.03)	0.81 (0.39-1.70)
	Secondary (9-12)	27 (23.1)	111 (47.6)	0.37 (0.20-0.69)*	0.33 (0.16-0.65)†
	College/University	13 (11.1)	20 (8.6)	0.99 (0.44-2.28)	0.87 (0.35-2.18)
Supplementary feeding commenced	<6 months (not yet started)	9 (7.7)	27 (11.6)	1.00	1.00
	Before 6 months	39 (33.3)	31 (13.4)	3.77 (1.60-9.20)*	1.16 (0.373.70)
	On 6 months	35 (29.9)	74 (31.9)	1.42 (0.60-3.34)	0.40 (0.12-1.27)
	After 6 months	34 (29.1)	100 (43.1)	1.02 (0.44-2.38)	0.30 (0.09-0.95)†
Hand washing after cleaning child's bottom	No	67 (57.3)	100 (42.9)	1.00	1.00
	Yes	50 (42.7)	133 (57.1)	0.56 (0.36-0.88)*	0.59 (0.35-0.99)†

** p < 0.05 on bivariate analysis* *† p < 0.05 on multivariate analysis*

IV. Discussion

In multivariate analysis, it was found that four factors remained independently significant to the risk of diarrhea, including, age of the child [AOR: 4.22, 95% CI: (1.36-13.14)], maternal education [AOR: 0.33, 95% CI: (0.16-0.65)], supplementary feeding commenced [AOR: 0.30, 95% CI: (0.09-0.95)], and hand washing after cleaning child's bottom [AOR: 0.59, 95% CI: (0.35-0.99)] (Table 4).

The results of this study indicated that the determinants of diarrhea as age of children, maternal education, supplementary feeding, hand washing after cleaning the child's bottom which had significant association to remain in each step.

From all socio demographic variables tested, age and maternal education remained significant after controlling other variables. The analysis showed that the age of the child had a significant effect on diarrhea, which is consistent with a study in Ethiopia (10). This study observed that the cases were mostly children between 6 and 11 months of age, in which there were 48 cases, making up the highest rate (41% of the total). Number of cases decreased in older children.

In general, the study showed that diarrhea was significantly associated with children in the age groups 6 - 11 months and 12 - 23 months. This finding is in agreement with another study in Ethiopia (11) and Ghana (12). The risk of diarrhea decreases sub-subsequently after 6 - 11 months; this is probably because the children begin to develop immunity to pathogens after repeated exposure (13).

The population policy of Ethiopia seeks to significantly increase female participation at all levels of the educational system. However, only 6 percent of females completed secondary education in Addis Ababa. The regression results supported the positive role of maternal education to under five diarrhea. The odds of having diarrhea associated with mothers' education remained significant even after controlling for all other variables. Based on this analysis those children whose mothers were at the secondary level of education are less likely to get diarrhea by 33% when compared to the reference illiterate.

It was found that mothers with higher education experienced better chance of a child being free of diarrhea, which is consistent with a cross sectional study in Ethiopia (14). Maternal education was significantly associated with diarrheal in children. The study in Ghana (15) indicated that the prevalence of diarrhea was lower among children of more educated mothers (secondary or higher) than among children of mothers with no or primary education. Educated mothers practice good hygiene, better child feeding and weaning practices. One study in Bangladesh showed that a child whose mother completed secondary school is 80% more likely to survive (16). But according to another study in Ethiopia (17), educational status of mothers or care takers was not statistically significant in relation to diarrhea.

Children who were partially on breast milk were more likely to have diarrhea than children who were exclusively on breast milk (18). In this study there were 34 cases (29.1%) and 100 controls (43.1%) that started supplementary feeding after 6 months. According to multivariate analysis in table 4, it was found that there was significant association between starting a supplementary food lately after 6 months and diarrhea. The finding of this study showed that children who were exclusively breastfed at the time of the survey were less likely to have diarrhea compared to less than six months' children who were not started supplementary food.

The odds of developing diarrhea was 59% less among children whose mothers washed their hands after cleaning their child's bottom. Studies showed the importance of hand washing in reducing the occurrence of childhood diarrhea (19).

V. Conclusions

The results of the study showed that the factors, namely age of children, maternal education, supplementary feeding and washing after cleaning the child's bottom were significantly associated with diarrhea among children less than five of age visiting Kotebe health center.

Overall, the finding is important for health intervention and support the view that investing in girls' education may have substantial benefits for child health. In this study, it has been found that education provides a solution. Specifically, secondary or above level of education for girls better be achieved in order to improve childhood diarrhea.

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The Need of Pharmacovigilance Activities in Yemen

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Abstract- Adverse drug reactions, medication errors and other drug-related problems are the leading causes of hospital-lisation and are associated with a huge economic burden and significant human suffering. This serious issue of medication therapy also contributes to morbidity and mortality. At present, the monitoring of adverse drug reactions was started in Yemen by establishing a pharmacovigilance centre in 2011. Till now there is no published information about its work , number of reports and how they process it. The country and public are facing with many safety problems related to drug smuggling, counterfeit drugs, improper and irrational use of drugs, importation of unnecessary drugs and medical errors. Therefore, it is necessary to make serious steps and active regulations in Yemen to ensure patients and public safety in relation to medicines use.

Keywords: adverse drug reaction, drug safety, pharm-acovigilance, safety monitoring, yemen.

GJMR-B Classification : NLMC Code: QV 738

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The Need of Pharmacovigilance Activities in Yemen

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Abstract- Adverse drug reactions, medication errors and other drug-related problems are the leading causes of hospitalisation and are associated with a huge economic burden and significant human suffering. This serious issue of medication therapy also contributes to morbidity and mortality. At present, the monitoring of adverse drug reactions was started in Yemen by establishing a pharmacovigilance centre in 2011. Till now there is no published information about its work , number of reports and how they process it. The country and public are facing with many safety problems related to drug smuggling, counterfeit drugs, improper and irrational use of drugs, importation of unnecessary drugs and medical errors. Therefore, it is necessary to make serious steps and active regulations in Yemen to ensure patients and public safety in relation to medicines use.

Keywords: adverse drug reaction, drug safety, pharmacovigilance, safety monitoring, yemen.

I. Introduction

Adverse drug reactions (ADRs) represent a serious health problem.[1] ADRs account for 3.2-7% of acute hospital admissions.[2,3] They cause morbidity, mortality, and longer duration of hospital stay[4] and increase hospital costs.[5] Over 770,000 people are injured or die each year due to adverse drug events.[6] A commonly quoted meta-analysis performed in the United States indicated that ADRs were ranged between the fourth and sixth most common cause of death in 1997.[7] The World Health Organization (WHO) defines an ADR as 'any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose'.[8]

Several previous studies have reported the incidence of ADRs. A prospective observational study from Iran identified that 11.75% of patients had experienced at least one ADR.[9] In another study done in Iran reported about 16.8% of patients had at least one ADR, and 2.9% of ADRs were identified as lethal.[10] A study in South India found that the overall incidence of ADRs was 9.8%. This included 3.4% ADR-related hospital admissions and 3.7% ADRs occurred during the hospital stay.[11] In Saudi Arabia, a retrospective study showed 54% of ADRs to be preventable. The prevalence per year ranged from 0.07% in 1993 to 0.003% in 1999.[12]

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In Nepal, the prevalence of ADRs was 0.86%. In addition, the male to female ratio of patients experiencing ADRs was 0.85, and 10.81% of the ADRs were severe.[13]

Pharmacovigilance is defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.[14] Thalidomide was the greatest tragedy of 1961 and led to the establishment of the drug regulatory mechanisms of today.[15] Pharmacovigilance is an arm of patient care that aims at making the best use of drugs and medicines for the treatment or prevention of disease without undesired effects. The history of international pharmacovigilance goes back as far as forty years, when the twentieth WHO assembly adopted a resolution to start an international system of monitoring ADRs.

The evolution of pharmacovigilance in recent years and its growing importance as a science have created much interest worldwide. Pharmacovigilance is based on sound scientific principles and is integral to effective clinical practice. The national pharmacovigilance centres have exercised significant influence on drug regulatory authorities. All developed countries have established national pharmacovigilance centres affiliated to the Uppsala monitoring centre in Sweden. Several developing countries requested WHO support and advice for building their pharmacovigilance centres.

All of the information about ADRs that is collected during the marketing phase of a drug is incomplete for five reasons: first, tests in animals are insufficient to predict human safety. Secondly, the limited number of patients are involved in clinical trials and carefully selected. Third, the licensing exposure of less than 5000 human subjects to a drug allows only more common ADRs to be detectable. Fourth, at least 30000 people required treatment with a drug to avoid missing of any patient. Fifth, information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) and drug interaction are often incomplete or unavailable; thus the high benefit of post-marketing surveillance to detect common ADRs.[15] There are differences between countries in the occurrence of ADRs and other drug-related problems. This may be due to differences in diseases, prescribing practices, genetics, diet, and culture. The drug manufacturing

processes, which in turn, influence pharmaceutical quality and composition, drug distribution and use, including indications, prescribed dose and availability as well as the use of traditional and complementary drugs (e.g., herbal remedies) are some of the other contributory factors that may pose specific toxicological problems when used alone and/or in combination with other drugs.[15]

Yemen is an Arab country located in the southern Arabian Peninsula. The Kingdom of Saudi Arabia, Oman, the Red Sea and the Arabian Sea border it. Yemen has a population of approximately 20 million, with more than 70% live in rural areas. The illiteracy rate is still high at about 55.7%. Yemen is a low-income country with a per capita Gross Domestic Product (GDP) of USD 659.[16] The total expenditure on health is not available at the present time, but the governmental contribution is about USD 256 million a year or $13 per capita and represents only 2% of the GDP. In general, the health services (either public or private) mainly focus major cities; though primary health centres/units and polyclinics are scattered throughout the whole country, including some rural areas. The statistical report (2003-2004) of the Ministry of Public Health & Population (MoPH) shows a total of 136 general hospitals (93 private), 470 polyclinics (341 private), 626 health centres (115 private), 2185 primary health care units, 380 maternity and child health centres, 1768 private pharmacies and a total of 4799 physicians (329 dentists and 974 specialists). In addition, there are a few non-governmental organisations (NGOs) and foreign medical missions.[16]

The local pharmaceutical industry is evolving gradually, covering only around 8% of the total market share. Medicines are imported via private sector agents and cover most of the country's needs.

There are critical health challenges in Yemen, including the high incidence of both communicable diseases (such as malaria, tuberculosis, schistosomiasis, sexually transmitted infections and vaccine-preventable diseases) and noncommunicable diseases (such as cardiovascular diseases, renal problems, cancer, and eye diseases). In addition, Yemen exhibits higher prevalence of lifestyle risk factors (including tobacco use, 'qat' chewing, malnutrition, injuries and accidents) and lacks the necessary sanitation (especially water sanitation). [17]

In Yemen, there is no systematic plan to monitor adverse drug reactions and drug-related problems. By the end of 2011 the SBDMA established a pharmacovigilance centre, till now there is no published information's about number of reports or how they process it.

This paper addressed the drug safety issues and highlights the justification of having pharmacovigilance activities in Yemen.

II. Drug Safety Problems in Yemen

Drug safety issues in Yemen include many serious problems that can have detrimental effects:

a) Smuggling of medicines

Studies have confirmed that the proportion of drugs entering Yemeni territory via illegal channels amounts to 60% of all imported medicines. According to Supreme Board of Drug and Medical Appliances (SBDMA), a society for consumer protection that monitors the use of 192 fake medicines, 176 different drugs are smuggled into Yemen, 46 of which are fake.[15] Medicines of doubtful quality, origin and expiry date are smuggled into the country through illegal channels and pose a serious threat to public health. Exposed to moisture and light during transport, their quality is also affected.. Sometimes these medicines become quite popular and the demand for them increases, as in the case of phenolphthalein laxative tablets, which are illegal in Yemen but continue to be sold.[18]

b) Fake drugs

Huge amounts of fake drugs flood Yemeni markets and pose serious health threats. Many Yemeni patients have become victims of fake drugs that are not appropriate for human use. Faking of medicines generally begins with the most sought after and rare drug types and then further expanded to other therapeutic categories Faking of medicines can only be identified by their side effects on the patients. There is no control over these drugs' safety, quality and effectiveness; SBDMA statistics indicate the presence of 46 different fake drugs on the Yemeni market. [18]

c) Policies of pharmaceutical companies in developing countries

Harmful drugs are still finding their way to developing countries. Some pharmaceutical companies market their products in developing countries, which are banned in their country of origin. These dangerous drugs generally sold without any concern for the health of the people, assisted by weak legislation and poor legal control of medicines in these countries.

One expert noted that the goal of the multinational companies that have planted their roots in developing countries is to achieve the highest level of profit regardless of humanitarian considerations. Pharmaceutical companies are not alone in using developing countries in this manner; contaminated food and radioactive waste were also shipped to developing countries for disposal.[20]

Ten thousand companies produce drugs in the world, but 90% of the drug trade is controlled by 100 companies, of which only 25 multinational companies account for 60% of international sales.[20] Forty-five percent of the poorest nations of the world are still

entirely dependent on imported medicines. The third world produces only 10% of all medicines.[20]

d) The lack of an active national drug policy

The primary goal of any policy is to ensure the availability of safe and effective, and quality medicines to meet the healthcare needs of the country.

Drug policy is an integral part of any comprehensive policy for health care. The formation of any national drug policy should take into account the health situation in the country, the medical care system, education and training of health care workers, possibilities for research and local production of medicines.[21]

The demand for medicines, distribution systems, possibilities for the evaluation and control of drugs, and international policies for pharmaceutical products are some of the other factors that should be considered at the time of formation of National Drug Policy. The need for a national drug policy and national system to monitor drug production and the presence of good governance to regulate matters relating to the implementation of drug control are some of the essential components of a robust functioning healthcare system.[21]

e) The lack of legislation

Till to date there is no legislation and regulation governing distribution and importation of drugs. There are no laws for the selection, registration, marketing and testing of medicines as well as no checks and balances to control importers and stop smuggling.

f) Weakness of local industry

The national pharmaceutical industry in Yemen is still emerging. It is still far short of the demand for domestic consumption. The eight existing local factories meet only 8.5% of the actual need in Yemen. They are unable to compete with world-famous brand names, and some of their products have lost credibility with Yemeni consumers. In addition, the local companies manufacture only medicines that will result in a quick profit and even unable to manufacture some life-saving drugs, worth mentioning are the therapeutic categories related to tuberculosis and cancer.

g) Registration of medicines without scientific criteria

The process of evaluation and registration of drugs should be based on the established requirements of quality, safety, efficacy, necessity and cost of drugs. The standards applied to the selection of the drugs should meet the following parameters:

1. Drugs must be selected based on scientific documentation.
2. The ratio between toxicity and effectiveness of a drug must be balanced by the severity of the disease.
3. The benefits of new drugs must be weighed against the availability of better therapeutic drugs in the market.
4. Combinations of drugs must be avoided unless and until it is clear that the compound has the advantages of both constituent drugs.
5. Definite medical need for new drug products should exist, and there should be medical justification of this need.
6. Drugs must be granted approval for a specific term (e.g., five years).
7. Price of drugs should be acceptable.[21]

h) Importation of unnecessary medicines

The private sector benefits from importing unsafe, nonessential and unnecessary medicines, merchandised by different means. World Bank study indicated that 41% of medicines imported in Yemen are unnecessary.[18] The importation of such medicines from abroad exacerbates Yemen's imbalance in payments. Yemen officially imports 13,000 products that cost around 50 million Yemeni riyal every year.[19]

i) Uncontrolled medicine distribution

The aim of planned medicine distribution is to meet public health needs. Distribution of medicines through agents and pharmacies should take into consideration the population density, the distance and transport requirements.

Governmental medicines generally distribute via central stores to government clinics without the consideration of real need. The conditions in which these drugs are stored leave them susceptible to the sun, the rain, and theft.

There is no control over the private sector, which distributes medicines through pharmacies far more efficiently than public-sector distribution. The private sector nurtures financial gains and sometimes distributes dangerous medicines.

j) Improper prescription of drugs by physicians

Some physicians prescribe medicines to patients unnecessarily. Others prescribe the wrong medicine or one that is not consistent with the diagnosis. At other times, unsafe medicines are being prescribed for minor cases; either in response to the patient's desire or because the physician believes that more intensive treatment is better. Some physicians even prescribe medicines without a diagnosis when their clinics are crowded.

k) Improper dispensing by pharmacists or salespeople

Some pharmacists dispense drugs incorrectly. They aim to sell medicines for profit without adherence to the basic standards of humanity and ethics of the profession of pharmacy. For example, they may switch the medicine prescribed by a physician with a similar drug available in the pharmacy. The pharmacist does not explain the indications, contraindications or side effects of the drug to the patient. Pharmacists sell prescription drugs, including sedative and antibiotics, without a prescription. Many workers in the pharmacies

do not have a higher education. They often lack adequate scientific understanding, and some of them know only the names and locations of the medicines on the shelves of the pharmacy.

l) Improper consumption

The increased demand for and widespread use of drugs (13,000 drugs are already registered) are very serious problems in Yemen. The widening network of drug distribution, pharmacies, and wholesale distributors and the increasing number of smuggled drugs add to the problem. Yemen imports medicines from 117 companies of 54 different countries.[19] All of this has led to a pharmaceutical consumption crisis with the following adverse consequences:

First, the irrational use of medicines, improper self-medication or the overuse of medicines prescribed by doctors as some doctors prescribe more than seven medicines in one prescription. Secondly, the adverse effects of these drugs are a major concern. The government is unable to test the quality and efficacy of these drugs due to the huge quantity of medicines coming from labs where the production of these medicines was not appropriately monitored. In addition, some doctors fail to prescribe proper medicines due to the marketing of one drug under multiple names and confusion over overlapping benefits of multiple medications.

m) Improper use of medicines by patients

The majority of patients do not follow the treatment prescribed by their doctors. Around 50% of patients do not use their medicines in the proper way. The patients' level of commitment to treatment decreases with the passage of time or after the disappearance of symptoms. In addition, sometimes the patient cannot buy the full course or the real medication prescribed, but they buy other medicines in the prescription, with the intention of treating the symptoms of the disease rather than the disease itself.

The high illiteracy rate of the Yemeni population makes it impossible for most people to read the instructions that come with their medicines. Thus, there is no awareness about indications, contraindications, side effects and expiry date.

n) Improper self-medication

Some patients treat themselves or their relatives without consulting a medical doctor. This can lead to adverse consequences for the health of Yemen's citizens as those who self-medicate are likely to be unaware of how to do so properly.

o) Lack of quality monitoring after marketing

The Yemeni medical authorities do not monitor the quality of medicines after marketing. Many ineffective drugs of poor quality are available in the market. Improper storage in most pharmacies can be detrimental to drug quality and effectiveness.

p) Lack of monitoring of ADRs

Monitoring and control of the harmful effects of drugs are one of the key components of any national drug policy. The prerequisites for monitoring of ADRs are:

- Measures to obtain information on medicines.
- Development of measures to take appropriate action on medicines causing adverse reactions in a timely manner.

First, doctors and pharmacists should report ADRs and notify health authorities and stakeholders. When a severe ADR is reported, scientific studies are advised to be conducted by medical and pharmacyological researchers. Second, a number of measures can be taken following notification of an ADR:

- Withdrawal of the drug from the market.
- Banning of selling and importing.
- Cancellation of registration.Destruction of existing stocks of the drug.Warning doctors, pharmacists and consumers.

q) Unethical promotion of medicines

Unethical promotion of medicines is norm of pharmaceutical companies. The representatives of these companies do not explain the risks that may arise from the use of their medications. Some companies promote their drugs only by distributing gifts and samples and thus create a real demand for ineffective or harmful medicines.

r) No oversight of medical prescriptions

A medical prescription is a legal document and must have accurate information, transparent with the seal of physician, including his/her name, telephone number, and license number. Doctors should be encouraged to write prescriptions using generic names.

s) Medical errors

The incidence of medical errors has increased in Yemeni hospitals due to ignorance or incompetence of medical staff. Many patients suffered due to medical and prescription errors, leading to morbidity and mortality. One must recognise that some complications that occur in the course of treatment cannot be avoided or predicted. The majority of medical errors do not result in legal action, and there is no strict oversight of the work of doctors and nurses by the medical authorities.

III. Conclusions

ADR-related monitoring and pharmacovigilance activities are still very poor in a country like Yemen, where drug safety problems are rampant. Pharmacovigilance might play an essential role in preventing and overcoming such problems. Yemen must institute a 'Pharmacovigilance Program' and set up Pharmacovigilance Centres in association with regulatory bodies such as SBDMA and medical and pharmacy schools

An awareness programme for local pharmaceutical companies, medical professionals and patients

to inform them about the detection and reporting of ADRs must be designed.

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Analytical Method for Estimation of Losartan by using UV - Spectrophotometer

By Dr. Safila Naveed
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Abstract- A simple, accurate, and economical least time consuming method for losartan method has been developed using Uv spectrophotometer.The assay is based on the UV absorbance maxima at about wavelength of 234nm using distilled water as solvent. Six sample of drug were dissolved in distilled water to produce solutions containing different brands of losartan. The absorbance of these six drugs were measured at 234 nm against the solvent blank and the assay were calculated by using the absorbance of active.This method can be used for the quality control QC quantitation and analysis of losartan in active and tablet formulations.

Keywords: *assay, losartan, UV pectrophotometer.*

GJMR-B Classification : *NLMC Code: QV 752, QV 745*

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Analytical Method for Estimation of Losartan by using UV – Spectrophotometer

Dr. Safila Naveed

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Keywords: assay, losartan, UV pectrophotometer.

I. Introduction

Losartan (fig 1) is a phenyl tetrazole substituted imidazole compound and it is a angiotensin II receptor blocker (ARB II) type I antagonist and it is used in the treatment of hypertension. Administration of Losartan results in a decrease TPR total peripheral resistance and cardiac venous return.

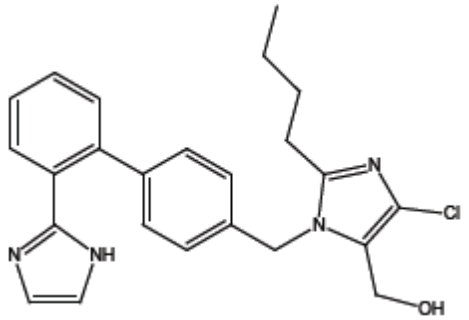

Figure 1 : Structure of Losartan

In literature, several methods have been described for analysis of Losartan potassium in API and formulations. Various methods are HPLC based [1,2], (CE) capillary electrophoresis [3], voltametric determination [4] and some are spectrophotometric [5-7].

But there is no single analytical method have been reported for determination of losartan as simple and economical like this method. Because I have used simple water for analysis of these all brandsand in very less time period I have analysed the drugs.we have done this types of assay for other drugs which will be useful for small scale laboratory and where expensive instrument not available we can easily find out these drugs in a very short period of time.

II. Experimental

a) Instrumentation

UV visible spectrophotometer (1601), Shimadzu double beam was used to analysis of spectra. The water is used as a solvent for active and formulations.

b) Wavelength Selection

About 100 ppm of losartan active solution was prepared in water. This solutions scanned in 200-400 nm UV region. The highest wavelength (λmax) was observed at 234 nm and therefor this wavelength was used for analysis of samples.

c) Standard solution of losartan

Accurately weighed 10 mg of losartan was transferred to a volumetric flask and add distilled water to produce 100 ml.the conc of solution is 100 ppm in 100 ml.

d) Sample Preparation of different brands

The six different brands AZA, COZAAR, LOSAAN, ZOSTAT, LOSARK and EZIDAY purchased from different pharmacies in Karachi, Pakistan. All tablets of each brand have same batch number and were labeled to conatin losartan 50 mg . All the six brands have 5 year shelf life.

The serial number as an identification of purchased brands are given in Table 1. Using 20 tablets of six different brand of losartan from the marketed sample were weighed and average mean were calculated. By calculating the average weighed powder of each brand equivalent to 10 mg of losartan was transferred in a volumetric flask containing small water then solution was sonicated for about 5 min and than make up volume upto 100 ml with water.Same procedure was repeat for all brands for preparation of solutions.

e) Procedure

After preparation of standard and sample solutions of different brands, strength of all solutions 100 ppm in 100 ml. By using 234 nm wavelength absorbance noted and calculate % assay of each drug.

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III. Results and Discussions

Pharmaceutical assay was carried out by using spectrophotometer on six brands of losartan tablets. Table-1 shows brand name, code, average weight of tablets ,amount for 100 ppm required and % assay of all six brands.

Results shows in figure 2 and table 1 . The percentage of AZA is found 101.0385%, for cozaar , losaan, zostat, losark, eziday 102.8077, 102.0385, 101.8077, 101.5 and 102.8846 respectively. The results shows that all drugs has percentages within the limit of USp/BP.

Table 1 : Assay of losartan

Brand Name	Code	Average wt of tablet mg	Wt for 100 ppm	Absorbance at 234 nm	% assay
AZA	LSR1	0.16	0.016	2.627	101.0385
cozaar	LSR2	0.156	0.015	2.673	102.8077
losaan	LSR3	0.153	0.015	2.653	102.0385
zostat	LSR4	0.18	0.018	2.647	101.8077
losark	LSR5	0.234	0.023	2.639	101.5
eziday	LSR6	0.175	0.017	2.675	102.8846

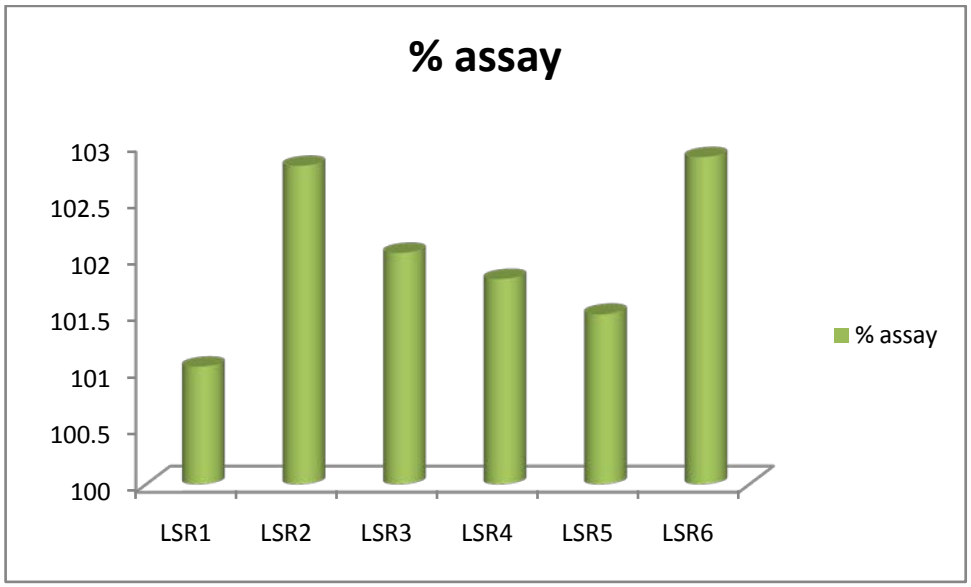

Figure 2 : % assay of different brands

IV. Conclusion

A simple, rapid, and economical UV method has been established for determination of losartan alone or in their formulations. This method has several advantages, including simple sample preparation and rapid analysis. It is suitable for analysis of antihypertensive agent losartan in their formulations in a single run, in contrast with previous published methods. This makes the method suitable for routine analysis in QC quality-control laboratories.

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Epilepsy: The Next Generation Drugs (A Review)

By Amit K. Shrivastava, Manish Dhar Dwivedi & Gulzar Alam

Abstract- Seizures are common and are treated in all branches of medicine. Approximately 10% of the population will have one or more seizures during their lifetime. Seizures are symptoms that occur in acute illness, ie, provoked seizures, or in epilepsy, ie, unprovoked seizures. Antiepileptic drugs (AEDs) are pharmacologic agents used to reduce the frequency of epileptic seizures. "Antiepileptic" drug is a misnomer, because these drugs are effective as symptomatic treatment of seizures, i.e., the symptoms of epilepsy, not as treatment of epilepsy itself. Recent discoveries in molecular biology and genetics have elucidated a genetic basis for some epilepsy syndromes, which will lead to new treatments. This review include new AEDs viz; Ganaxolone, Eslicarbazepine acetate, Fluorofel-bamate, Huperzine A, Carisbamate (RWJ- 333369), Brivaracetam (ucb 34714), 2-Deoxy-D-glucose, Retigabine, T2000 , T2007, Valrocemide, Tonabersat (SB- 220453), YKP3089, Propyl isopropyl acetamide, JZP-4, ICA- 105665, NAX-5055, Perampanel and Valpromide.

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Epilepsy: The Next Generation Drugs (A Review)

Amit K. Shrivastava [α], Manish Dhar Dwivedi [σ] & Gulzar Alam [ρ]

Abstract- Seizures are common and are treated in all branches of medicine. Approximately 10% of the population will have one or more seizures during their lifetime. Seizures are symptoms that occur in acute illness, ie, provoked seizures, or in epilepsy, ie, unprovoked seizures. Antiepileptic drugs (AEDs) are pharmacologic agents used to reduce the frequency of epileptic seizures. "Antiepileptic" drug is a misnomer, because these drugs are effective as symptomatic treatment of seizures, i.e., the symptoms of epilepsy, not as treatment of epilepsy itself. Recent discoveries in molecular biology and genetics have elucidated a genetic basis for some epilepsy syndromes, which will lead to new treatments. This review include new AEDs viz; Ganaxolone, Eslicarbazepine acetate, Fluorofel-bamate, Huperzine A, Carisbamate (RWJ-333369), Brivaracetam (ucb 34714), 2-Deoxy-D-glucose, Retigabine, T2000 , T2007, Valrocemide, Tonabersat (SB-220453), YKP3089, Propyl isopropyl acetamide, JZP-4, ICA-105665, NAX-5055, Perampanel and Valpromide.

I. Epilepsy: The Next Generation Drugs (A Review)

Epilepsy affects approximately 50 million people worldwide, with an annual incidence of 50 to 70 cases per 100,000 population (1). Epilepsy is a common chronic neurologic disorder that affects 1% to 3% of the population, and almost two million people in the United States alone (2). Seizures are more common than is generally appreciated; almost 10% of the population will have at least one seizure during their lifetime (3). Epileptic syndromes are defined by many factors, including type of seizure, age at onset of seizures, family history, and findings at physical examination, ictal and interictal electroencephalography (EEG), and neurologic imaging. Overall, complex partial seizures are the most common seizure type across age groups. Generalized seizures are more common in children, and partial seizures are more common in adults. Incidence of partial seizures remains constant at 20 per 100,000 population from infancy until age 65 years, when it increases sharply. Incidence of generalized tonic-clonic seizures is high at age 1 year (15 per 100,000 population), then declines until age 10 to 14 years and remains at that rate until it again rises at age 65 years. Incidence of absence seizures is 11 per 100,000 population from age 1 to 10 years, with uncommon onset after age 14 years. Myoclonic seizures are common during the first year of life, but decline after that (4-6).

Epilepsy is a disease characterized by spontaneous recurrence of unprovoked seizures. Seizures and epilepsy are different disorders, and the terms should not be used interchangeably. It is not accurate to refer to seizures as epilepsy, although "seizure disorder" refers to epilepsy. Seizures are symptoms, whereas epilepsy is a disease characterized by recurrent seizures. Seizures can result from diseases with the enduring tendency to seizures characteristic of epilepsy.

During the last decade, the two mainstays of epilepsy treatment, epilepsy surgery and antiepileptic drug (AED) therapy, have made great advances, resulting predominantly from advances in imaging techniques and the development of new AEDs. New AEDs have been developed to provide drugs with fewer side effects and greater efficacy than those currently available. We review some of the recent drugs which acquired a well renowned position for the treatment of epilepsy. In this article, we review the mechanisms of action, efficacy, pharmacokinetic properties, and adverse reactions of the new AEDs.

II. Ganaxolone

IUPAC Name: 3α-hydroxy-3β-methyl-5 α -pregnan-20-one.

It is 3β-methyl analog of the neurosteroid allopregnanolone, a metabolite of progesterone. Like other related neurosteroids, ganaxolone is not believed to have nuclear hormone activity and cannot be biotransformed to metabolites with such activity. A new submicron particulate formulation enhances bioavailability of ganaxolone compared to the oral suspension used in earlier studies (7).

Ganaxolone is a positive allosteric modulator of GABAA receptors with potency and efficacy comparable to those of its endogenous neurosteroid analog allopregnanolone (8). Ganaxolone has protective activity in diverse rodent seizure models, including clonic seizures induced by pentylenetetrazol (PTZ) and bicuculline, limbic seizures in the 6 Hz model, and amygdale and cocaine-kindled seizures (9,10).

In addition to the anticonvulsant activity, there is evidence that neurosteroids can retard the development of spontaneous recurrent seizures in some animal models of epileptogenesis, and therefore they have antiepileptogenic actions in such models (11).

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Ganaxolone has been tested in more than 900 subjects in Phase I and Phase II studies and was found to be generally safe and well-tolerated across the dose range used (for Phase II studies, up to 1875 mg/day in adults and up to 54 mg/kg/day in pediatric subjects), with divided daily dosing. The new studies show that ganaxolone at a dose of 1500 mg/day is efficacious, safe and well-tolerated as adjunctive therapy for partial seizures for adults, with no evidence of significant toxicities or weight gain in the Phase II program.

III. Eslicarbazepine Acetate

IUPAC Name: (S)-(−)-10-acetoxy-10,11 dihydro-5H-dibenz/b,f/azepine-5-carboxamide

Eslicarbazepine acetate is a third-generation, singleenantiomer (with one chiral center) member of the long-established family of first-line dibenz/b,f/azepine AEDs. Eslicarbazepine acetate was designed with the aim of improving efficacy and safety in comparison with the structurally related drugs carbazepine and oxcarbazepine. Eslicarbazepine acetate formerly known as BIA 2-093, is a novel CNS-active compound. Eslicarbazepine acetate shares with carbazepine and oxcarbazepine the basic chemical structure of a dibenzazepine nucleus with the 5-carboxamide substituent, but is structurally different at the 10,11-position (12).

Mechanistically, Eslicarbazepine acetate behaves as a potent blocker of voltage-gated sodium channels through interference with site 2 of the channel, and does not bind to receptors for benzodiazepines, gamma amino butyric acid (GABA) and glutamate (13,14). Eslicarbazepine is the main active metabolite of eslicarbazepine acetate and represents about 95% of the total systemic drug exposure following oral administration of eslicarbazepine acetate. Single and multiple ascending dose studies in healthy male volunteers showed that Eslicarbazepine acetate is rapidly converted to the active metabolite or 10,11 dihydro-10-hydroxy-5Hdibenz[b,f]azepine-5 carboxamide. The precise mechanism of action of eslicarbazepine acetate is not known. In vitro electrophysiological studies indicate that both eslicarbazepine acetate and eslicarbazepine competitively interact with site 2 of the inactivated state of a voltage-gated sodium channel, preventing its return to the active state and repetitive neuronal firing. Eslicarbazepine acetate inhibits release of the neurotransmitters or neuromodulators glutamate, GABA, aspartate and dopamine in rat striatal slices (15).

IV. Fluorofelbamate

IUPAC Name: 2-phenyl-2-fluoro-1,3 propanediol dicarbamate

Fluorofelbamate is an analogue of felbamate designed to have the same broad spectrum anticonvulsant activity as felbamate without the serious adverse effects of the latter. In particular, the presence of a fluorine atom in the 2-position of the propanediol chain in the Fluorofelbamate molecule is intended to prevent the production of atropaldehyde, the reactive toxic metabolite of felbamate (16).

Preliminary evidence suggests that Fluorofelbamate acts, at least in part, by decreasing responses to GABA, kainate and N-methyl-D-aspartate (NMDA), and by reducing voltage-dependent sodium currents (17). Other actions are likely to contribute to its pharmac-ological effects in animal models. Fluorofelbamate shows protective activity against ischemia- and hypoxia-induced neuronal damage in a variety of models in vivo and in vitro (18).

V. Huperzine A

Huperzine A is a sesquiterpene Lycopodium alkaloid isolated from Chinese club moss (Huperzia serrata), also known as the Chinese folk medicine Qian Ceng Ta, Traditionally used in China for swelling, fever and inflammation, blood disorders and schizophrenia. Huperzine A is used in China for the treatment of Alzheimer's disease. It is classified as a dietary supplement by the FDA. Huperzine A was active against subcutaneous pentylenetetarzol- but not maximal electroshock-induced-induced seizures following p.o. administration to Swiss-Webster mice, with peak anticonvulsant activity at 1 h (19). At doses of 1, 2, and 4 mg/kg, a maximum of 62.5% protection was observed. Huperzine A is a potent, highly specific and reversible inhibitor of acetylcholinesterase, with comparable potency to physostigmine, galantamine, donepezil and tacrine (20). Huperzine A also produces dose dependent increases of norepinephrine and dopamine in rat cortex when administered i.p. or locally. A study of neuro-protective, antiepileptogenic, and anticonvulsant effects of huperzine A in a rodent model of traumatic brain injury is in progress.

VI. Carisbamate (RWJ-333369)

IUPAC Name: S-2-O-carbamoyl-1-o-chlorophenyl- ethanol

Carisbamate (RWJ-333369) is a novel anticonvulsant, with one chiral center, initially developed by SK Biopharmaceuticals, under development for the treatment of epilepsy. It shows a broad spectrum of activity in preclinical models of epilepsy and has demonstrated a favorable efficacy and tolerability profile in a Phase II clinical trial. Phase III clinical trials are in progress. Carisbamate has been found to possess potent and a broad spectrum of activity in a battery of acute rodent seizure models (21). At 10 and 30 mg/kg i.p., carisbamate significantly reduced the frequency of spontaneous recurrent seizures in the kainate post-status epilepticus model of temporal lobe epilepsy, and

compared to topiramate was able to completely suppress spontaneous recurrent seizures in a larger proportion of rats in the study (22).

VII. Brivaracetam (ucb 34714)

Brivaracetam (ucb 34714) is a novel chiral (with two chiral) high-affinity synaptic vesicle protein 2A (SV2A) ligand which also displays inhibitory activity at neuronal voltage-dependent sodium channels (23). The function of SV2A is not well established; however, a strong functional correlation between SV2A binding affinity and anticonvulsant potency in animal models of both focal and generalized epilepsy has been established (24). Brivaracetam is currently in Phase III development for epilepsy.

Preclinical studies have shown that brivaracetam is more potent and efficacious than levetiracetam in animal models of seizures and epilepsy (25). Two Phase III, double-blind, randomized, multicenter, historical-controlled trials (N01276, NCT00698581 and N01306, NCT00699283) are ongoing to evaluate the efficacy and safety of brivaracetam (50 mg/day) as conversion to monotherapy in patients with uncontrolled focal epilepsy.

VIII. 2-Deoxy-D-Glucose

2-Deoxy-D-glucose, a glucose analogue differring from normal glucose only by removal of a single hydroxyl group at the 2 position, is a glycolytic inhibitor with novel anticonvulsant and disease-modifying antiepileptic properties. 2-Deoxy-D-glucose is preferentially delivered to brain regions in response to energy demand by an exquisitely regulated system of neurovascular coupling involving vascular cells, perivascular neurons, and astrocytes which precisely increases regional blood flow and glucose supply within seconds and within a few hundred microns in neural circuits experiencing increased activity (26), as occurs during seizures. 2-Deoxy-D-glucose, after activity-dependent uptake into cells through glucose transporters, undergoes phosphorylation by hexokinase at the 6 position to 2-deoxy-D-glucose- 6-phosphate. 2 Deoxy-D-glucose-6-phosphate is transiently ''trapped'' in cells. Glycolytic inhibition by 2-deoxy-D-glucose is a novel anticonvulsant mechanism with both acute and chronic actions. The chronic antiepileptic actions of 2-deoxy-Dglucose against progression of kindled seizures have been associated with its actions as a glycolytic inhibitor acting to repress expression of brain-derived neurotrophic factor (BDNF) and receptor tyrosine protein kinase B (TrKB). Preclinical toxicology and pharmacokinetic studies are planned in anticipation of filing of an IND with the FDA. Because 2-deoxy-D-glucose undergoes rapid absorption and uptake after oral and parenteral administration but has a relatively short half-life, a slow-release formulation is currently in development.

IX. Retigabine

IUPAC Name: N-[2-amino-4-(4-fluorobenzylamino)-phenyl]- carbamic acid ethyl ester

Retigabine is a unique antiepileptic compound that was identified during screening at the National Institutes of Health in 1991, and is currently being developed by Valeant Pharmaceutcials, USA. Early investigations showed that retigabine could activate a voltage-sensitive, neuron-specific outward potassium current that was later identified as the M-current mediated by KCNQ (Kv7) channels. Upon activation by excitatory input, the M-current opposes subsequent depolarizing inputs, reducing the likelihood of raising the membrane potential above the action potential threshold. Retigabine reduces neuronal excitability by primarily enhancing the activity of the KCNQ2/KCNQ3 (Kv7.2/Kv7.3) Secondary mechanisms of action include potentiation of GABA-evoked currents in cortical neurons via activation of GABAA receptors containing β2 or β3 subunits. Channels (27). A Phase II, multicenter, randomized, double blind, placebo controlled dose-ranging trial (Study 205) evaluated retigabine 600, 900, or 1200 mg/day as adjunctive therapy in adults with partial-onset seizures. Two recently completed double-blind, placebo controlled Phase III studies have confirmed the dose dependent efficacy of 600—1200 mg/day retigabine and demonstrated that 600—900 mg/day is an appropriate initial target dose range for retigabine as adjunctive therapy in adults with partial-onset seizures.

a) T2000

IUPAC Name: 1,3-dimethoxymethyl-5,5-diphenylbarbituric acid

T2000 is a member of the barbiturate class of drugs. T2000 is a prodrug and is rapidly metabolized to monomethoxymethyl-5, 5-diphenylbarbituric acid (MMMDPB) and 5,5 diphenylbarbituric acid. Earlier studies performed on isolated neural systems in aplysia and the hippocampus of the rat have shown that 5,5-diphenylbarbituric acid, the major metabolite of T2000, suppresses neural repetitive firing in both systems at concentrations lacking significant effects on GABA neurotransmission. These effects may be attributable to enhancement of outgoing membrane potassium current. Studies of 5,5 diphenylbarbituric acid on cat motor nerve terminal function show a suppression of repetitive discharges similar to the effects of phenytoin, a compound which acts on sodium channels in the nerve membrane. T2000 is being investigated for the treatment of essential tremor, myoclonus dystonia and epilepsy.

b) T2007

IUPAC Name: Sodium 5,5-diphenylbarbiturate

T2007 is a member of the barbiturate class of drugs. T2007, the sodium salt of 5,5 diphenylbarbituric

acid, a new barbiturate salt, is presently under development by Taro Pharmaceuticals for treatment of epilepsy and essential tremor. T2007 and prodrugs of DBP like T2000 (1,3-dimetoxymethyl-5, 5-diphenylbarbituric acid), retain useful pharmacological activities at dosages that are not accompanied by sedation

X. Valrocemide

IUPAC Name: N-valproyl glycinamide

Valrocemide was selected from a series of N-valproyl derivatives of GABA and glycine because of its favorable pharmacokinetic and anticonvulsant activity profiles in preclinical screening models(28). In mice and rats, Valrocemide protects against seizures induced by maximal electroshock test (MES), pentylenetetrazol (PTZ), bicuculline (BIC) and picrotoxin (PIC). In healthy subjects, VLR exhibits linear pharmacokinetics after single oral doses ranging between 250 and 4000 mg and multiple doses ranging between 250 and 1000 mg three times daily(29-31). Recently, a new controlled-release formulation of valrocemide has been developed and in a crossover study conducted in 18 healthy subjects was found to produce equivalent AUC exposure to an immediate release formulation of valrocemide, with a relative bioavailablity of 88% (90% CI, 81—96%).

a) Tonabersat (SB-220453)

IUPAC Name: (3S-cis)-N-(6-Acetyl-3,4-dihydro-3-hydroxy- 2,2-dimethyl-2H-1 benzopyran-4-yl)-3-chloro-4- fluorobenzamide

Tonabersat, formerly know as SB-220453, is a chiral (with two asymmetric centers) novel benzoylaminobenzopyran compound with potent anticonvulsant activity. Tonabersat selectively and specifically binds a unique stereo selective site in the CNS, thought to be at the neuronal gap junction. As such, tonabersat represents a 'first-in-class' neurotherapeutic that does not act via any established anticonvulsant mechanisms. In a number of animal seizure models, tonabersat, at doses of 1-10 mg/kg orally, exhibited activity comparable in efficacy and potency with current AEDs. The pain associated with migraine headache is believed to be associated with activation of the trigeminal vascular system. Stimulation of the fifth cranial (trigeminal) nerve results in a reproducible increase in carotid blood flow and a concomitant reduction in carotid vascular resistance. The effects of tonabersat on trigeminal nerve stimulation were investigated in the anaesthetised cat. Continuous i.v. administration of tonabersat at 3.4 or 11.5_mol/h produced a dose-dependent and time-related reduction in the effects of trigeminal nerve stimulation(32).

b) Ykp3089

YKP3089 is a novel compound with broad-spectrum anticonvulsant activity under clinical development at SK Life Science. YKP3089 protects against MES induced seizures in mice with an ED50 of 9.8 mg/kg i.p., and in rats with an ED50 of 1.9 mg/kg p.o. In the sc Met seizures model, YKP3089 given ip inhibited the clonic seizures in mice and rats, with ED50 values of 28.5 and 13.6 mg/kg, respectively. YKP3089 was also effective against seizure induced by picrotoxin with an ED50 of 34.5 mg/kg in mice. YKP3089 was effective in reducing significantly the expression of stage 5 seizures in the hippocampal kindled rat (ED50 = 16.4 mg/kg). YKP3089 was effective in the mouse 6 Hz psychomotor seizure model at 22, 32 and 44 mA, with ED50 values of 11.0, 17.9 and 16.5 mg/kg, respectively. YKP3089 also protects against lithium-pilocarpine-induced intractable seizures in rats (ip) (ED50 = 7.0 mg/kg) (33).

XI. Propylisopropyl Acetamide (PID)

PID is a chiral (with one chiral center) CNS-active constitutional isomer of valpromide, the CNS-active corresponding amide of valproic acid(34). PID is not metabolized in animals to its corresponding acid (propylisopropylacetic acid) and therefore can be regarded as a metabolically stable constitutional valpromide isomer.

a) JZP-4

IUPAC Name: [3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine)]

JZP-4, is a novel, potent sodium and calcium channel blocker, structurally related to lamotrigine and endowed with broad spectrum anticonvulsant activity. The anticonvulsant profile of JZP-4 was established in a battery of well defined seizure and epilepsy models, with tests performed by the Anticonvulsant Screening Project at the National Institute of Neurological Disorders and Stroke (NINDS) and internally. The results from these studies suggest that JZP-4 possesses a broad-spectrum of activity (35). JZP-4 has inhibitory effects on both sodium and calcium channels, which collectively represent its presumed mechanism of action. JZP 4's antiepileptic properties are currently being evaluated in proof-of-concept study in humans. Single oral doses of JZP-4 ranging from 50 to 200 mg are compared to a single oral dose of Lamotrigine (325 mg) in their ability to decrease cortical excitability following transcranial magnetic stimulations in healthy male volunteers (36).

b) ICA-105665

ICA-105665 is a chemically novel (although its chemical structure has not yet been disclosed) highly selective opener of neuronal KCNQ (Kv7) potassium channels. The activity of ICA-105665 has been tested in a range of seizure and epilepsy models at Icagen and by the Anticonvulsant Screening Project of the National Institute of Neurological Disorders and Stroke. The primary effect of this compound is to shift the voltage-dependence of KCNQ2/Q3 channel activation to more negative potentials. As a result, KCNQ2/3 current is

enhanced at voltages near the threshold for activation at which this channel typically has significant effects on membrane excitability (Table 3). This functional increase in KCNQ2/3 current is expected to be greater for neurons with more depolarized resting membrane potentials and/or high firing rates. ICA-105665 has been tested for its ability to reduce the photoparoxysmal EEG response in epilepsy patients with photosensitivity using well established standardized methods (37).

c) NAX-5055

Neuropeptides are potent modulators of neuronal excitability. The endogenous neuropeptide galanin is widely expressed in the CNS and has been recognized as a potential anticonvulsant agent. NAX 5055 is one of the prototype compounds that have been extensively evaluated. In proof of- principle studies, NAX 5055 has validated the technology platform by demonstrating long-lasting and dose-dependent activity in the 6 Hz seizure model following i.v., i.p. s.c. and oral administration (38). NAX 5055 also exhibited potent efficacy in other models of epilepsy and pain.

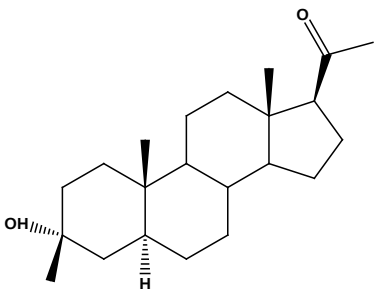
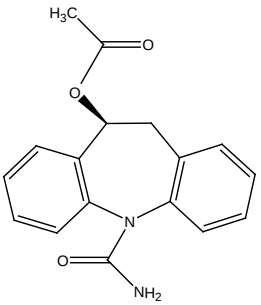
d) Perampanel (E2007)

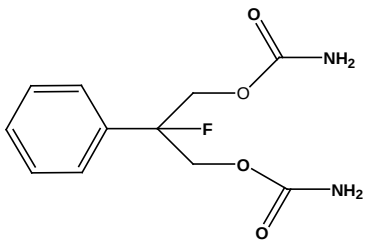
Perampanel (E2007) is an orally active, noncompetitive, and highly selective AMPA (□-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid)-type glutamate receptor antagonist currently in Phase III development for epilepsy. Preclinical studies have demonstrated that perampanel attenuates a spectrum of seizure types in rodent models of seizures and epilepsy (39). Three Phase III, randomized, placebo-controlled, adjunctive therapy, double-blind, multicenter, multinational studies in patients 12 years of age or older with refractory partialonset seizures are ongoing. These studies (NCT00699582, NCT00699972 and NCT00700310) are designed to evaluate the efficacy and safety of perampanel (2, 4, 8, and 12 mg/day) over a 12-week maintenance period.

XII. Valpromide

Valpromide, the corresponding amide of valproic acid. Valpromide possesses two stereogenic carbons in its structure and has been commercially available as an anxiolytic drug in the form of a racemic mixture (Nirvanil®) in France. A recent study showed that racemic- valpromide (1 mM) drastically inhibits human brain crude homogenate myo-inositol-1-phosphate (MIP) synthase activity. Valpromide was found to reduce the MIP synthase activity by an apparent competitive mode of inhibition at concentrations within the therapeutic range of valproic acid (Ki = 0.18 mM) (40). These data support the clinical use of valpromide in bipolar disorder. The development of valpromide (as racemate or individual stereoisomer) as a new potentially non-teratogenic and nonhepatotoxic CNS agent that is more potent than valproic acid, may offer a valuable alternative to valproic acid for the treatment of patients with bipolar disorder, epilepsy and neuropathic pain.

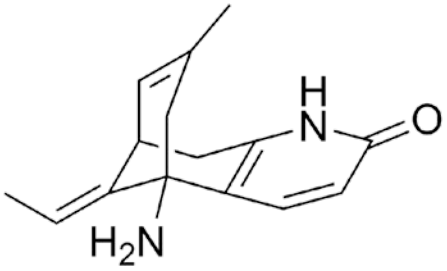
Table 1 : Chemical structures of antiepileptic drug

 3α-hydroxy-3β-methyl-5 α -pregnan-20-one	 (S)-(-)-10-acetoxy-10,11 dihydro-5H-dibenz/b,f/azepine-5-carboxamide
Ganaxolone	**Eslicarbazepine acetate**

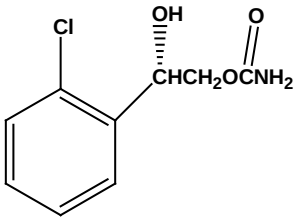


2-phenyl-2-fluoro-1,3 propanediol dicarbamate

Fluorofelbamate

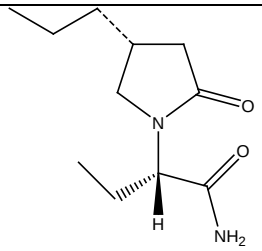


Huperzine A



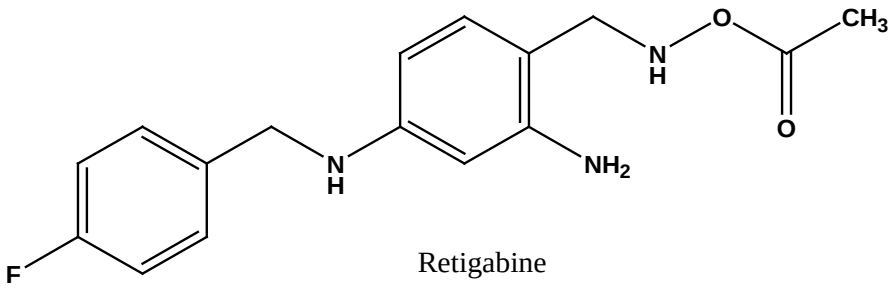
S-2-O-carbamoyl-1-o-chlorophenyl- ethanol

Carisbamate (RWJ-333369)



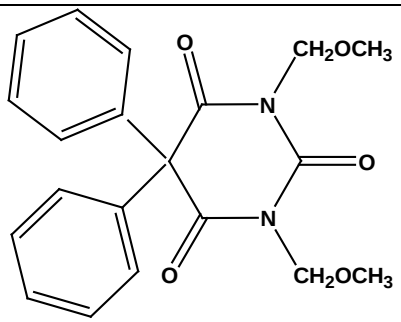
N-[2-amino-4-(4-fluorobenzylamino)-phenyl]- carbamic acid ethyl ester

Brivaracetam (ucb 34714)



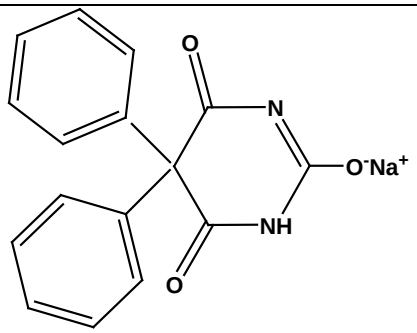
Retigabine

Retigabine



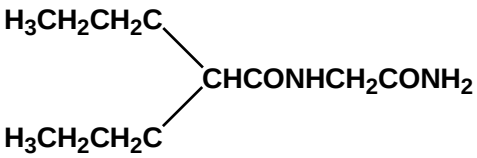
1,3-dimethoxymethyl-5,5- diphenylbarbituric acid

T2000



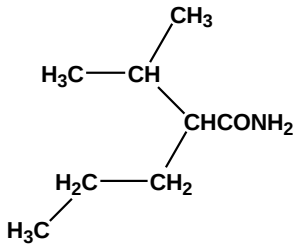
Sodium 5,5- diphenylbarbiturate

T2007



N-valproyl glycinamide

Valrocemide



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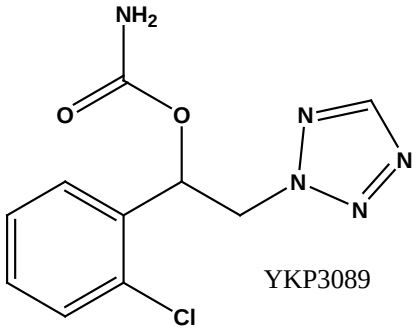
Propylisopropyl acetamide



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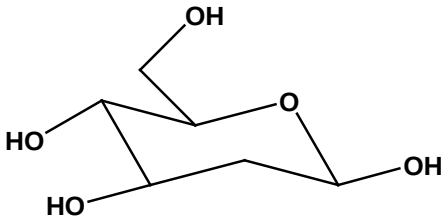
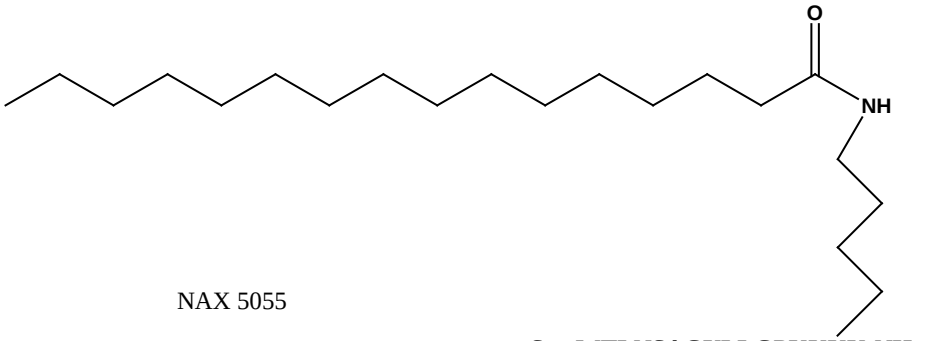


6-Hydroxymethyl-tetrahydro-pyran-2,4,5-triol

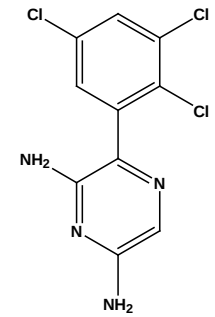
2-Deoxy-D-glucose



NAX 5055

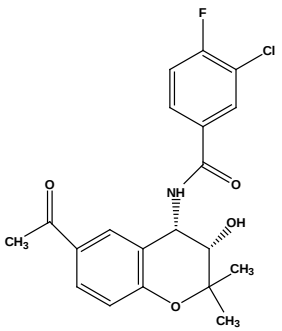
Sar-WTLNSAGYLLGPKKKK-NH_2

NAX 5055



4 (3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine)

JZP-4



[(3S-cis)-N-(6-Acetyl-3,4-dihydro-3-hydroxy- 2,2-dimethyl-2H-1 benzopyran-4-yl)-3-chloro-4- fluorobenzamide

Tonabersat (SB-220453)

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An Insight into the Genetic Study and Pathogenesis of the Colorectal Cancer

By Tapan Behl, Ishneet Kaur, Heena Goel & Rajesh K. Pandey
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Abstract- Colorectal cancer is defined as the cancer of the large intestine or the rectum – thus attributing to some other names related to this cancer such as – bowel cancer or rectal cancer, depending on the site where the tumor has occurred. It mostly begins as a benign tumor with then turns into a carcinoma.Colon cancer and rectal cancer are related in terms of their genetics and thus are studied together as allied tumors. Although some other factors such as age and lifestyle are also concerned with the progression of this cancer, a minority group of people acquire it because of certain genetic predisposition, which is focused upon in this review. Initially it was thought only to occur because of certain mutations in a specific gene called adenomatous polyposis coli (APC) gene which are responsible for initiating the characteristic events which lead to the progression of this tumor.The cases affected by this pathway were called the LOH group. But further researches concluded that there is another different pathway which can lead to the occurrence of this tumor apart from the one briefly stated above.

Keywords: adenomatous polyp, APC gene, LOH group, MSI-positive group, beta-catenin.

GJMR-B Classification : NLMC Code: QZ 20.5, QZ 40, QZ 52

Strictly as per the compliance and regulations of:

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Tapan Behl [α], Ishneet Kaur [σ], Heena Goel [ρ] & Rajesh K. Pandey [ω]

Abstract- Colorectal cancer is defined as the cancer of the large intestine or the rectum – thus attributing to some other names related to this cancer such as – bowel cancer or rectal cancer, depending on the site where the tumor has occurred. It mostly begins as a benign tumor with then turns into a carcinoma.Colon cancer and rectal cancer are related in terms of their genetics and thus are studied together as allied tumors. Although some other factors such as age and lifestyle are also concerned with the progression of this cancer, a minority group of people acquire it because of certain genetic predisposition, which is focused upon in this review. Initially it was thought only to occur because of certain mutations in a specific gene called adenomatous polyposis coli (APC) gene which are responsible for initiating the characteristic events which lead to the progression of this tumor.The cases affected by this pathway were called the LOH group. But further researches concluded that there is another different pathway which can lead to the occurrence of this tumor apart from the one briefly stated above. The rest of the cases which were affected by this second pathway were named as the MSI-positive group. Since diagnostic techniques for detecting this cancer, like colonoscopy, as well as its treatment by employing chemotherapy are readily available, it should be considered prime priority to get to know about this tumor at the early stage.If diagnosed earlier, this cancer can be checked upon and thus could make the concerned person survive for a longer time with improved quality life.

Keywords: adenomatous polyp, APC gene, LOH group, MSI-positive group, beta-catenin

I. Introduction

Colorectal cancer – also known as colon cancer or rectal cancer – is a lethal type of cancer which might occur in the colon or rectum (or both). It initiates as a small benign (non-carcinogenic) bundle of outgrown cells called adenomatous polyp which might then, with time, turn into a carcinogenic cluster and metastasize to other regions of the body such as adjacent lying lymph nodes, liver, lungs and various other sites. Almost 50% of the total cases of primarily benign colorectal neoplasm progress to develop metastatic cancer. It constitutes approximately 10-15% cases of all cancers prevalent and is the second most preeminent cause of deaths, after lung cancer, occurring due to any type of cancer in the western countries[1]. Advancing age is, so far, regarded as the greatest risk-factor for being prone to the occurrence of this tumor. Apart from this, the reasons for the development of this tumor might be both- environmental as well as genetic. Despite of the availability all the required diagnostic technologies as well as suitable treatments, the mortality rate of the patients suffering with this cancer remains quite high. Thus, it is generally advised to detect the tumor at earliest stages and commencing the treatment as soon as possible so that best possible recovery could be achieved because diagnosing the tumor at its advanced stages have shown to leave very little possibility of the survival of the patient even after sufficient treatment [2].

II. Epidemiology

Colorectal cancer is one the most common form of cancer found in the different populations worldwide. It affects both the sexes but the incidence rate in men is almost double that of the women. The high risked population is affected by colon cancer and rectal cancer in 2:1 ratio i.e., colon cancer occurrence is double than the rectal cancer. This fact is supported by an epidemiological data of the colorectal cancer collected by conducting a study in The United States. According to this study, about 136,830 new cases of colorectal cancer were diagnosed in a specific year out of which, 96,830 cases were of colon cancer while the remaining 40,000 cases were of rectal cancer, thus, giving a clear indication of the accuracy of the above estimated ratio [3]. In Germany, about 57,000 cases of colorectal cancer are reported every year. Thus, the data suggests that this cancer constitutes the most common type of cancer prevalent in Germany, even encompassing other most severely prevalent cancers in the world like breast cancer (whose prevalence in Germany is only 46,000 cases per year) and lung cancer (amounting up to just 37,000 cases per year). The mortality rate among the total cases of colorectal cancer reported in Germany is around 26,500 deaths per year [4]. The global statistical epidemiological data of colorectal cancer is extremely greater than this above stated data. Also, it has been seen that different geographical regions are affected differently by this cancer due to the variations in the environment as well as diverse dietary patterns among various populations.

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This fact is supported by the evidencethat countries like Australia, New Zealand, Europe and North America have the highest incidence rate of this cancer in the world whereas in some regions of Africa and South-Central Asia, the occurrence rates are very low [5].

III. Signs and Symptoms

In the initial stages of the tumorigenesis, the colorectal cancer may remain assymptomatic i.e., the patient may exhibit no signs or symptoms. When presentation of signs and symptoms start, they generally depend on the site of the occurrence of tumor and the extent to which it has metastasized.On the advent of the production of characteristic sign and symptoms, the patient may experience the following listed adversities: -

- Alterations in the bowel movement are the first manifestation of the colorectal cancer which is generally characterized by –
  - ✓ melena (black and tarry stools) due to the oxidation of the blood which was present along with stools
  - ✓ Prolonged and severe constipation in which the bowel movement may be blocked to a great extent due to the narrowing of the colon or rectum
  - ✓ Unrelenting diarrhea
  - ✓ Chronic bleeding in the colon or rectum which may lead to anemia
  - ✓ Presence of mucus in the stools
  - ✓ Increased urge of defecating frequently
  - ✓ Feeling of unempty bowel even after defecating
- Sensation of discomfort, pain, bloating or fullness in the abdomen. Cramps may also be experienced by the patient. In some cases, a lump may also be felt in any region of abdomen.
- The patient may experience loss of appetite and may continuously feel nauseous and frequent vomiting may also occur.
- Fatigue or weakness in the whole body (especially the limbs) may occur due to the anemia caused by severe blood loss.
- Weight loss and fever are another such common features associated with almost all the cases of colorectal cancer.
- Perforation caused by some kind of piercing in the bowel is a medical emergency which requires immediate surgery because it might lead to further complications such as peritonitis and formation of abscess [6-8].

IV. Causes

Age is attributed to be the foremost cause of the development of colorectal cancer even in persons having any other kind of predisposition for its development. In as estimate made, about 9 people out of 10 diagnosed with colorectal cancer are above 50 years of age. However, the exact reason behind the occurrence of this cancer in old-aged people is still unknown [9]. Apart from age, there are numerous other factors which may attribute to the progression and development of colorectal cancer. These causes are described below: -

- *Dietary factors:* It has been long speculated that diet of a person may contribute for some causes which may lead to the progression of colorectal cancer.People having high intake of animal fats and proteins in their daily diet have been linked with the increased risk of developing this cancer but no such confirmation has been given in the medical literature. Some studies have shown that consumption of red meat frequently becomes the promoter of some reasons which further lead to initiation of the tumor while some other studies found no such relation. While some researchers consider fat to be the major harbinger of this cancer, others consider proteins as the same. Apart from the fats and proteins themselves, another group of researchers point out to the way of these substances getting cooked, especially when exposed to very high temperature during the processes of broiling and barbecuing – which results in the production of certain carcinogenic substances as the end products, to be the affecters which need to be considered as the main reasons for the connection between these biomolecules andthe progression of colorectal cancer [10-11].
- *Lifestyle factors:* Smoking is considered as one of the foremost reasons for the development of colorectal cancer. A study conducted on the current and former smokers against life-long non-smokers (which represent a group of people who have consumed at the most 100 cigarettes in their whole lifetime) concluded that the development of colorectal cancer is directly proportional to the duration of smoking i.e., the more a person smoked, the more he is at an increased risk for developing this cancer. According to an estimate, a person who has been associated with smoking for more than 40 years or the people who are not able to quit smoking before the age of 40 are more prone to the progression of colorectal cancer by an increased rate of about five times as compared to non-smokers. Also, the people who quit smoking are related to a decreased risk of developing this cancer, thus validating the factor of smoking as a risk-factor [12]. Heavy alcohol consumption is another such factor. Although the mechanism which alcohol results in the progression of colorectal cancer is not yet clear, it has been speculated that the end product of its metabolism viz., acetaldehyde is responsible for

it. This fact is supported by the evidence of its carcinogenic properties in the animal models [13]. Also, lack of sufficient physical exercise is also associated with an increased risk for developing colorectal cancer [14].

- *Genetic factors:* People who are normally associated with a family which is having a history of colorectal cancer are considered to be at a greater risk than the ones who do not have any such report. Genetic factors accounts for upto 20% of the total cases of colorectal cancer worldwide. Thus, this factor cannot be easily ruled out when considering various risk-factors and causes of this cancer. In case of colorectal cancer, a few inherited conditions, in which there is an early development of the colon polyps due to some genetic predisposition, like familial adenomatous polyposis (FAP) – also known as Gardner's syndrome [15], MYH- associated polyposis (MAP) [16], Turcot's syndrome, Peutz-Jagher's syndrome, juvenile polyposis and Cowden's diseaseare associated with an increased risk of developing colorectal cancer, if not treated at the earliest stages. But the most common inherited condition associated with this cancer is called the hereditary non-polyposis colorectal cancer (HNPCC) – which is also known as Lynch syndrome. HNPCC alone accounts for approximately 2 to 4% of the total cases of the colorectal cancer [17]. According to the genetic studies, there may be two pathways which can be associated with the genetic events occurring in any individual which lead to the progression of colorectal cancer due to the genetic factors. These two identified pathways are described as follows: -

i. LOH group: - LOH stand for loss on heterozygosity. This group of people constitutes approximately 80% of the total cases of colorectal cancer which are caused due to various genetic factors. The characteristic feature of this group is a type of chromosome mutation which results in aneuploidy (i.e., a mutation in which the diploid number of chromosomes are either less or more than the normal value). It is also associated with numerous allelic losses. The tumor caused in this group is activated by WNT/Wingless pathway which is initiated by a mutation caused in the APC (adenomatous polyposis coli) gene [18].

ii. MSI-positive group: - MSI-positive stands for microsatellite instability-positive. This group of people accounts forabout 15% of the remaining cases of colorectal cancer associated with genetic predisposition. The reason for this type of instability caused in the gene is attributed to mismatching repair of the DNA.The tumor formation in this group is reported to occur due to the accumulation of beta-catenin (which acts as the main transcriptional activator of the carcinogenesis occurring in colorectal cancer), which is acquired by a catenin stabilizing mutation caused in the beta-catenin gene [19].

V. Pathogenesis

The formation of adenomatous polyps in the colon and rectum, which occurs due to mutation caused in the APC gene, is considered to be the basic initiator for the progression of colorectal cancer. These mutations can either be inherited or acquired. Apart from the common mutation of APC gene (which occurs in the majority of cases of colorectal cancer). There may be some other rare mutations such as mutations in beta-catenin gene, various other genes which are anologues of APC such as AXIN1 [20], AXIN2 [21], TCF7L2/TCF4 [22] or NKD1 [23], which might also lead to the progression of colorectal cancer.These various mutations result in dysfunction of the concerned gene which further leads to the activation of certain mechanisms which, at first, lead to the formation of benign adenomatous polyps and then further accounts for the progression of these benign polyps into advanced adenomas which can metastasize into various other sites of the body. After the formation of a malignant tumor, the stage of the tumor decides whether it can be cured or not, e.g., when the tumor is at the initial-most stage (when the invasive cancer is still confined within the walls of the colon and has not broken out of it – known as stage I and II), the tumor is curable. However, if it is left untreated at this stage, anyhow, it could grow further and spread into the lymph nodes lying in the nearby region and mark the advent of stage III of the tumor. This stage is curable in upto approximately 73%of the cases by the employment of adjuvant chemotherapy. After this stage, the tumor rapidly metastasizes into various sites (near as well as distant) of the body which is represented as stage IV of the tumor.Although many advancements have been done till now in the process of chemotherapy, stage IV of the tumor remains incurable [24-27].The various events in the pathogenesis of colorectal cancer can be listed as follows: -

- *Mutational activation of tumor suppressor gene:* The foremost step of the pathogenesis of colorectal cancer is the occurrence of mutations in the various genes associated with tumor suppression. These mutations lead to the dysfunctioning of the concerned genes which, due to their linkage with some other pathways, lead to the progression of the colorectal tumor. The various key factors involved in this process are as follows: -

- ✓ *APC:* APC gene is regarded as the most important factor in the progression of colorectal cancer. The activation of the Wnt signaling pathway – which is responsible for the regulation of gene transcription in the cells, due to the mutations caused in the APC gene, is regarded as the primary step in the tumor formation. The mutation in the APC gene results in the loss of both APC alleles which is further responsible for full-length proteins getting lost in the tumor cells. This leads to various types of physiologic alterations which disturbs the homeostasis of the processes which are responsible for the regulation of growth of the epithelial cells in the colon e.g., Transcription, cell cycle succession, migration, differentiation, and apoptosis. Thus, due to the critical role of APC gene in the monitoring of cell growth in colon because of its ability to control the levels of beta-catenin in the cytoplasm, any kind of mutation may result in unchecked growth and transcriptional activities in the cells present there [28-29]. APC is a component of the degradation complex which degrades beta-catenin, whose role is to bind with certain members of T-cell factor–lymphocyte enhancer factor family and create a specific transcription factor which results in the activation of cellular growth factors. Thus, normal APC gene helps in keeping a check over the levels of beta-catenin in the cytoplasm of the cell whereas mutated APC loses its capability to perform any such regulatory function. Hence, in the absence of normal regulatory mechanisms, the levels of beta-catenin goes up resulting in an unchecked activation of Wnt signaling pathway whose outcome is the initiation of tumor formation [30-31].
- ✓ *TP53:* TP53 gene, also known as tumor protein-53 gene, is another gene whose mutations are responsible for the progression of colorectal cancer. The somatic mutations occurring in this gene are considered to the most common cause of the development of many types of cancers including colorectal cancer. The p53 protein is well-known for its anti-proliferative activity in response to various types of stress conditions as well as during normal physiologic conditions. Therefore, inactivation of this protein is the prime target of various carcinogens. Its inactivation is primarily achieved by single base substitution and allele loss [32]. In the progression of colorectal cancer, this event holds the second most important spot after the inactivation of APC gene. The loss of both the alleles of TP53 gene is generally achieved by a two-step mutation process in which the first step is a missense mutation which inactivates the transcriptional activity of p53 and the second step involves a deletion on the chromosome 17p (where this gene is located) which results in the loss of the second allele. The inactivation of TP53 is often linked with the conversion of large benign adenomas into invasive carcinomas, due to the occurrence of both the events at the same point of time [33-34].
- ✓ *TGF-beta tumor suppressor pathway:* The inactivation of TGF-beta is normally the next step in the progression of colorectal cancer. In one-third of the cases of colorectal cancer, inactivation of TGRBR2 occurs due to somatic mutations. The tumors associated with the mismatch repair defect, distinctive frameshift mutations are responsible for the inactivation of TGRBR2 due to the presence of polyadenine repetition. 50% of the cases comprising of wild-type mismatch repair, the tumor suppressor pathway of TGF-beta is ceased due to inactivating nature of the missense mutations which occur in this gene by affecting the TGRBR2 kinase domain. Another way by which the mutations (or deletions) could affect this pathway is by causing alterations in the SMAD4 component of the TGF-beta pathway or the other transcription factors involved along with it e.g., SMAD2 and SMAD3. The events of mutations occurring in this gene and the consequential alterations in the pathways have been associated with the transition of adenomas to high grade dysplasia or evolution of carcinoma [35].

- *Activation of oncogene pathways:* The activation of several oncogene pathways such as MAPK signaling pathway is normally observed in the patients having colorectal cancer. These pathways are said to be responsible for the overexpression and overactivation of various cellular proliferation processes owing to their location at the downstream of various growth-factor receptors, which includes one of the most important growth factor responsible for excessive cellular proliferation in the colorectal cancer viz., epidermal growth factor [36]. The activation of the below given two oncogene pathways is said to mainly influence and play an important part in the pathogenesis of the colorectal cancer: -

- ✓ *RAS and BRAF:* Among the various oncogenes which play a vital role in the progression of colorectal cancer, the two most important are – RAS and BRAF. The oncogenic mutations caused in RAS and BRAF pathways result in the activation of MAPK (mitogen-activated protein

kinase) signaling pathway in about 37% and 13% of the cases of colorectal cancer, respectively. The mutations in the RAS pathway, particularly in KRAS, leads to the activation of GTPase activity which is responsible for conducting signals to the RAF whereas the mutations caused in BRAF implicates the signaling of BRAF serine-threonine kinase activity, which is further responsible for the activation of MAPK signaling pathway. BARF mutations can be easily detected evn in small-sized polyps and occur more frequently in hyperplastic polyps, serrated adenomas and proximal colon cancers, as compared to the RAS mutations. A medical condition named as hyperplastic polyplosis syndrome is observed in the patients having large sized and large number of hyperplastic lesions. Observations show that these type of patients are at a much greater risk of developing colorectal cancer than the people without hyperplastic polyplosis syndrome because the histologic examinations of the patients suffering from this syndrome shows that the progression of disease in such patients occurthrough an intermediate lesion formation having a serrated luminal borderline around it [37-39].

✓ *Phosphatidylinositol 3-kinase:* The somatic mutations in PI3KCA, which encodes the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), are observed in almost one-third of the total cases of the colorectal cancer, hinting that this might also play a vital role in the progression of this cancer. Apart from this, some less commonly occurring mutationsare also found in place of PI3KCA, such as loss of PTEN – which inhibits the signaling of PI3K, while others include amplification of insulin receptor substrate 2 (IRS2), upstream activation of the signalling PI3K, co-amplification of AKT and PAK4, which act as the downstream mediators of PI3K signaling pathway. Thus, all the mutations and the alterations caused by them are said to play some part, which is not yet well-understood, in the progression of the colorectal cancer [40-41].

- *Genomic changes and tumor progression:* According to an initially formulated model of the transformation of adenoma to carcinoma, the role of specific tumor-promoting mutations, which are acquired progressively, was considered. This model states the occurring of certain mutations which governs the characteristics properties of tumor-progression, such as the presence of regional or distant metastases. But according to the results of full-genome examination of the sequences in some patients, from primary benign cancers of colorectal cancer to the distant malignant metastases, there was no new mutations observed during the process of metastases. This observation resulted in the speculation that a new mutation is not necessarily required for the progression of primary tumor into a metastasized form which could progress to distant sites. Also, the finding of the presence of all metastasized mutations in the primary lesions, leads to the conclusion that seeding of metastatic form of tumor is very rapid, which may even take a time span ofless than 2 years to progress into a final staged tumor from a primary one [42].
- *Growth factor pathways:* Various growth factor pathways are considered to be responsible for the cell proliferation process occurring in tumor.

✓ *Aberrant regulation of prostaglandin signaling:* Activation of prostaglandin signaling pathway is considered to be prime step in the development of an adenoma in the pathogenesis of colorectal cancer. Mainly inflammation and mitogen-associated upregulation of COX-2 (which is an inducible enzyme which is responsible for the regulation of the synthesis of prostaglandin E2 – a robustly linked agent in the progression of colorectal cancer) are considered to be responsible for the activation of this pathway. An enhanced activity of prostaglandin E2 is also observed when there is a loss of 15-PGDH (15- prostaglandin dehydrogenase – an enzyme whose role in the process of catalytic degradation of prostaglandin E2 is very critical). An elevation in the levels of COX-2 (cyclooxygenase-2) is seen in almost two-third of the patients of colorectal cancer and a loss of 15-PGDH is observed in about 80% of the cases of colorectal cancer, thus indicating that this mechanism is surely linked in some way in the progression of this cancer. Also, some clinical studies conducted showed that the inhibition of COX-2 is successfully able to suppress the development of new adenomas and also restricts the growth of already formed ones, thus validating its connection with the colorectal cancer [43-44].

✓ *Epidermal growth factor receptor:* EGF (epidermal growth factor) is a soluble protein which exhibits trophic effects on the cells of the colon. Important signaling role has been illustrated for the EGF receptor in a particular subgroup of the colorectal cancer cases. This signaling via EGF receptor (EGFR) is regulated by the activation of MAPK and PI3K signaling pathways (which are already described above).Other clinical studies done lately also

conclude that the anti-EGFR therapies showed no effect on the alterations caused due to various mutations such as in KRAS, BRAF and the p110 subunit of PI3K. Further researches are going on to discover more about the connection and mechanism of EGFR in the progression of colorectal cancer [45-46].

- ✓ *Vascular endothelial growth factor:* VEGF (vascular endothelial growth factor), which is mainly involved in the states of injury, various inflammatory processes and also during the normal physiologic growth of the tissue, is said to be key mediator for the formation of new stromal blood vessels – a process called angiogenesis. The role of angiogenesis has been well established by various clinical studies in the growth of the tumor in colorectal cancer. According to a clinical study, treatment of a patient suffering from advanced colorectal cancer with anti-VEGF antibody bevacizumab lead to an increase of 4.7 months in the average estimated total survival period of the patient viz., 15.6 months after being treated with regular standard therapy. Although much research has been done in this regard, more studies are still need to be done to identify the molecular distinctions between which gain assistance by this treatment and the rest who do not [47].

VI. Conclusion

From all the above discussions we conclude that the genetic factors play a critical role in determining the progression of colorectal cancer in any person. The genetic predisposition of any patient of colorectal cancer might be held responsible for the tumorigenesis. The pathogenesis of colorectal cancer involves the mutations of various significant genes which are responsible for the physiology of various proteins and factors responsible for the regulation of cellular proliferation processes in the colon and rectum. Overactivation of any of these factors results in the progression of the formation of a primary tumor and its transition from a benign adenoma to an invasive carcinoma. Thus, these events should be checked upon by diagnosis as early as possible so that appropriate treatment could be started well in time and at the stage where it could be successfully treated.

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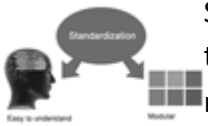

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- In case, the chairperson needs to be replaced then consent of 2/3rd board members are required and they are also required to jointly pass the resolution copy of which should be sent to us. In such case, it will be compulsory to obtain our approval before replacement.
- In case of "Difference of Opinion [if any]" among the Board members, our decision will be final and binding to everyone.

"

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1. General,

2. Ethical Guidelines,

3. Submission of Manuscripts,

4. Manuscript's Category,

5. Structure and Format of Manuscript,

6. After Acceptance.

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The **Introduction** should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable to comprehend and calculate the purpose of your study without having to submit to other works. The basis for the study should be offered. Give most important references but shun difficult to make a comprehensive appraisal of the topic. In the introduction, describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will have no attention in your result. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here. Following approach can create a valuable beginning:

- Explain the value (significance) of the study
- Shield the model - why did you employ this particular system or method? What is its compensation? You strength remark on its appropriateness from a abstract point of vision as well as point out sensible reasons for using it.
- Present a justification. Status your particular theory (es) or aim(s), and describe the logic that led you to choose them.
- Very for a short time explain the tentative propose and how it skilled the declared objectives.

Approach:

- Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done.
- Sort out your thoughts; manufacture one key point with every section. If you make the four points listed above, you will need a least of four paragraphs.

- Present surroundings information only as desirable in order hold up a situation. The reviewer does not desire to read the whole thing you know about a topic.
- Shape the theory/purpose specifically - do not take a broad view.
- As always, give awareness to spelling, simplicity and correctness of sentences and phrases.

Procedures (Methods and Materials):

This part is supposed to be the easiest to carve if you have good skills. A sound written Procedures segment allows a capable scientist to replacement your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt for the least amount of information that would permit another capable scientist to spare your outcome but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section. When a technique is used that has been well described in another object, mention the specific item describing a way but draw the basic principle while stating the situation. The purpose is to text all particular resources and broad procedures, so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step by step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

- Explain materials individually only if the study is so complex that it saves liberty this way.
- Embrace particular materials, and any tools or provisions that are not frequently found in laboratories.
- Do not take in frequently found.
- If use of a definite type of tools.
- Materials may be reported in a part section or else they may be recognized along with your measures.

Methods:

- Report the method (not particulars of each process that engaged the same methodology)
- Describe the method entirely
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures
- Simplify - details how procedures were completed not how they were exclusively performed on a particular day.
- If well known procedures were used, account the procedure by name, possibly with reference, and that's all.

Approach:

- It is embarrassed or not possible to use vigorous voice when documenting methods with no using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result when script up the methods most authors use third person passive voice.
- Use standard style in this and in every other part of the paper - avoid familiar lists, and use full sentences.

What to keep away from

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings - save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part a entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Carry on to be to the point, by means of statistics and tables, if suitable, to present consequences most efficiently.You must obviously differentiate material that would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matter should not be submitted at all except requested by the instructor.

Content

- Sum up your conclusion in text and demonstrate them, if suitable, with figures and tables.
- In manuscript, explain each of your consequences, point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation an exacting study.
- Explain results of control experiments and comprise remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or in manuscript form.

What to stay away from

- Do not discuss or infer your outcome, report surroundings information, or try to explain anything.
- Not at all, take in raw data or intermediate calculations in a research manuscript.
- Do not present the similar data more than once.
- Manuscript should complement any figures or tables, not duplicate the identical information.
- Never confuse figures with tables - there is a difference.

Approach

- As forever, use past tense when you submit to your results, and put the whole thing in a reasonable order.
- Put figures and tables, appropriately numbered, in order at the end of the report
- If you desire, you may place your figures and tables properly within the text of your results part.

Figures and tables

- If you put figures and tables at the end of the details, make certain that they are visibly distinguished from any attach appendix materials, such as raw facts
- Despite of position, each figure must be numbered one after the other and complete with subtitle
- In spite of position, each table must be titled, numbered one after the other and complete with heading
- All figure and table must be adequately complete that it could situate on its own, divide from text

Discussion:

The Discussion is expected the trickiest segment to write and describe. A lot of papers submitted for journal are discarded based on problems with the Discussion. There is no head of state for how long a argument should be. Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implication of the study. The purpose here is to offer an understanding of your results and hold up for all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of result should be visibly described. Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved with prospect, and let it drop at that.

- Make a decision if each premise is supported, discarded, or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."
- Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work
- You may propose future guidelines, such as how the experiment might be personalized to accomplish a new idea.
- Give details all of your remarks as much as possible, focus on mechanisms.
- Make a decision if the tentative design sufficiently addressed the theory, and whether or not it was correctly restricted.
- Try to present substitute explanations if sensible alternatives be present.
- One research will not counter an overall question, so maintain the large picture in mind, where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

- When you refer to information, differentiate data generated by your own studies from available information
- Submit to work done by specific persons (including you) in past tense.
- Submit to generally acknowledged facts and main beliefs in present tense.

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Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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